PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]Activelle® *LD*

0.5 mg Estradiol and
0.1 mg Norethindrone acetate, USP

Film-coated tablets

Estrogenic Hormones/Progestin

Novo Nordisk Canada Inc.
101-2476 Argentia Road
Mississauga, Ontario
L5N 6M1 Canada

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RECENT MAJOR LABEL CHANGES

Not applicable

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Activelle® *LD* (estradiol/norethindrone acetate) is indicated for:

- The treatment of moderate to severe vasomotor symptoms occurring in naturally or surgically induced estrogen deficiency states associated with menopause.

  Activelle® *LD* is recommended only in women with intact uteri since the regimen includes a progestin to prevent endometrial hyperplasia.

1.1 Pediatrics

Pediatrics (< 18 years of age): Activelle® LD is not indicated for use in a pediatric population. Safety and effectiveness in pediatric patients have not been established.

2 CONTRAINDICATIONS

- Patients with known hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the product monograph.
- Liver dysfunction or disease as long as liver function tests have failed to return to normal
- Known, suspected, or past history of estrogen-dependent or progestin-dependent malignant neoplasia (e.g. endometrial cancer)
- Endometrial hyperplasia
- Known, suspected, or past history of breast cancer
- Undiagnosed abnormal genital bleeding
- Known or suspected pregnancy
- Active or past history of arterial thromboembolic disease (e.g. stroke, myocardial infarction, coronary heart disease)
- Active or past history of confirmed venous thromboembolism (such as deep vein thrombosis or pulmonary embolism) or active thrombophlebitis
- Partial or complete loss of vision due to ophthalmic vascular disease
- Porphyria
- Classical migraine
- Breastfeeding

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial examined the health benefits and risks of oral combined *estrogen plus progestin* therapy (n=16,608) and oral *estrogen-alone* therapy (n=10,739) in postmenopausal women aged 50 to 79 years.[1-3]

The *estrogen plus progestin* arm of the WHI trial (mean age 63.3 years) indicated an increased risk of *myocardial infarction* (MI), *stroke, invasive breast cancer, pulmonary emboli* and *deep vein thrombosis* in postmenopausal women receiving treatment with combined conjugated equine estrogens (CEE, 0.625 mg/day) and medroxyprogesterone acetate (MPA, 2.5 mg/day) for 5.2 years compared to those receiving placebo.[1]

The *estrogen-alone* arm of the WHI trial (mean age 63.3 years) indicated an increased risk of *stroke* and deep *vein thrombosis* in hysterectomized women treated with CEE-alone (0.625 mg/day) for 6.8 years compared to those receiving placebo. [2]

Therefore, the following should be given serious consideration at the time of prescribing:

- Estrogens with or without progestins **should not** be prescribed for primary or secondary prevention of cardiovascular diseases.
- Estrogens with or without progestins should be prescribed at **the lowest effective dose** for the approved indication.
- Estrogens with or without progestins should be prescribed for **the shortest period** possible for the approved indication.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Activelle® *LD* is a low-dose continuous combined Hormone Replacement Therapy (HRT) product intended for use in women with intact uteri. For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration should be used.

In women with amenorrhea and not taking HRT or women in transition from another continuous combined HRT product, treatment with Activelle® *LD* may be started on any convenient day. In women in transition from sequential HRT regimens, treatment should start right after their withdrawal bleeding has ended.

4.2 Recommended Dose and Dosage Adjustment

One tablet of Activelle® *LD* (estradiol 0.5 mg and norethindrone acetate 0.1 mg) should be taken orally once a day without interruption, preferably at the same time every day. Patients should be re-evaluated within 3-6 months after initiation of treatment, to assess response to treatment.

4.5 Missed Dose

If the patient has forgotten to take a tablet, the tablet should be taken as soon as possible

within the next 12 hours. After 12 hours the tablet should be discarded and next dose taken at the normal time. Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting.

5 OVERDOSAGE

Symptoms of overdose
Numerous reports of ingestion of large doses of estrogen products and estrogen-containing oral contraceptives by young children have not revealed acute serious ill effects. Overdosage with estrogen may cause nausea, vomiting, breast discomfort, fluid retention, bloating or vaginal bleeding in women. Progestin (e.g. norethindrone acetate) overdosage has been characterized by depressed mood, tiredness, acne and hirsutism.

Treatment of overdose
Treatment should be symptomatic.

For management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Nonmedicinal Ingredients
Oral	Film-coated tablet 0.5 mg estradiol (as estradiol hemihydrate) and 0.1 mg norethindrone acetate	Hydroxypropylcellulose, hypromellose, lactose monohydrate, maize starch, magnesium stearate, talc, triacetin

Activelle® *LD* tablets are white, round, biconvex, film-coated tablets engraved with NOVO 291 on one side and APIS on the other side. The tablets are available in calendar dial packs of 1x28 tablets or 3x28 tablets. Each tablet contains estradiol 0.5 mg (as the hemihydrate) and norethindrone acetate 0.1 mg.

7 WARNINGS AND PRECAUTIONS

General
For the treatment of postmenopausal symptoms, Hormone Replacement Therapy (HRT) should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk.

Carcinogenesis and Mutagenesis

Breast Cancer
Available epidemiological data indicate that the use of combined *estrogen plus progestin* by postmenopausal women is associated with an increased risk of invasive breast cancer.

In the *estrogen plus progestin* arm of the WHI trial, among 10,000 women over a one-year period, there were:

- 8 more cases of invasive breast cancer (38 on combined HRT versus 30 on placebo).[1]

The WHI study also reported that the invasive breast cancers diagnosed in the *estrogen plus progestin* group were similar in histology but were larger (mean [SD], 1.7 cm [1.1] vs 1.5 cm [0.9], respectively; P=0.04) and were at a more advanced stage compared with those diagnosed in the placebo group. The percentage of women with abnormal mammograms (recommendations for short-interval follow-up, a suspicious abnormality, or highly suggestive of malignancy) was significantly higher in the *estrogen plus progestin* group versus the placebo group. This difference appeared at year one and persisted in each year thereafter.[3]

In the *estrogen-alone* arm of the WHI trial, there was no statistically significant difference in the rate of invasive breast cancer in hysterectomized women treated with conjugated equine estrogens versus women treated with placebo.[2]

It is recommended that estrogens with or without progestins not be given to women with existing breast cancer or those with a previous history of the disease (see 2 CONTRAINDICATIONS).

There is a need for caution in prescribing estrogens with or without progestins for women with known risk factors associated with the development of breast cancer, such as strong family history of breast cancer (first degree relative) or who present a breast condition with an increased risk (abnormal mammograms and/or atypical hyperplasia at breast biopsy).

Other known risk factors for the development of breast cancer such as nulliparity, obesity, early menarche, late age at first full term pregnancy and at menopause should also be evaluated.

It is recommended that women undergo mammography prior to the start of HRT treatment and at regular intervals during treatment, as deemed appropriate by the treating physician and according to the perceived risks for each patient.

Taking estrogens with progestins may increase the density of breast tissue, potentially adversely affecting the capability of mammography to detect breast cancer.

The overall benefits and possible risks of hormone replacement therapy should be fully considered and discussed with patients. It is important that the modest increased risk of being diagnosed with breast cancer after 4 years of treatment with combined estrogen plus progestin HRT (as reported in the results of the WHI trial) be discussed with the patient and weighed against its known benefits.

Instructions for regular self-examination of the breasts should be included in this counselling.

Endometrial Hyperplasia & Endometrial Carcinoma

The risk of endometrial hyperplasia and carcinoma is increased when estrogens are administered alone for prolonged periods to women with intact uteri. The role of a progestin, when combined with estrogen, is to prevent endometrial hyperplasia/carcinoma in women with

intact uteri. The addition of a progestin for at least 12 days per cycle in non-hysterectomised women reduces this risk.

In the WHI study, endometrial cancer rates were low and were not increased by 5 years of *estrogen plus progestin* exposure (hazard ratio 0.83 [adjusted 95% CI 0.29-2.32])[1]. Because endometrial cancer has a relatively low incidence rate, the incidence of endometrial hyperplasia is used as a surrogate endpoint in clinical studies.

In a double-blind, randomised, multi-center study, 1,176 healthy postmenopausal women aged 44 years and older without evidence of endometrial abnormalities were given 12 months of treatment with continuous combined regimens of 1 mg E2 with 3 different doses of norethindrone acetate (NETA; 0.1 mg, 0.25 mg, 0.5 mg). All 3 doses, have shown similar incidences of endometrial hyperplasia at the end of 12 month study, and were significantly better at reducing the incidence of endometrial hyperplasia relative to E2 alone ($p<0.001$), based on 988 endometrial biopsies.

A second study assessed the endometrial thickness resulting from treatment with Activelle® *LD* (0.5 mg E2/0.1 mg NETA; n=185) versus a formulation containing 0.5 mg E2/0.25 mg NETA (n=173) or placebo (n=177). At 24 weeks, there were no differences between the groups in mean change of endometrial thickness, as evaluated by transvaginal ultrasound.

Ovarian Cancer
Some recent epidemiologic studies have found that the use of hormone replacement therapy (estrogen-alone and estrogen plus progestin therapies), in particular for 5 or more years, has been associated with an increased risk of ovarian cancer.

Cardiovascular
The results of the Heart and Estrogen/progestin Replacement Studies (HERS and HERS II) and the Women's Health Initiative (WHI) trial indicate that the use of *estrogen plus progestin* is associated with an increased risk of coronary heart disease (CHD) in postmenopausal women.[1,4,5] The results of the WHI trial indicate that the use of *estrogen-alone* and *estrogen plus progestin* is associated with an increased risk of stroke in postmenopausal women.[1,2]

WHI Trial Findings
In the combined *estrogen plus progestin* arm of the WHI trial, among 10,000 women over a one-year period, there were:

- 8 more cases of stroke (29 on combined HRT versus 21 on placebo)
- 7 more cases of CHD (37 on combined HRT versus 30 on placebo).[1]

In the *estrogen-alone* arm of the WHI trial of women with prior hysterectomy, among 10,000 women over a one-year period, there were/was:

- 12 more cases of stroke (44 on *estrogen-alone* therapy versus 32 on placebo)
- No statistically significant difference in the rate of CHD.[2]

HERS and HERS II Findings
In the Heart and Estrogen/progestin Replacement Study (HERS) of postmenopausal women with documented heart disease (n=2763, average age 66.7 years), a randomized placebo-controlled clinical trial of secondary prevention of coronary heart disease (CHD), treatment with 0.625 mg/day oral conjugated equine estrogen (CEE) plus 2.5 mg oral

medroxyprogesterone acetate (MPA) demonstrated no cardiovascular benefit. Specifically, during an average follow-up of 4.1 years, treatment with CEE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the hormone-treated group than in the placebo group in year 1, but not during the subsequent years.[4]

From the original HERS trial, 2,321 women consented to participate in an open label extension of HERS known as HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. After 6.8 years, hormone therapy did not reduce the risk of cardiovascular events in women with CHD.[5]

Blood Pressure
Women using hormone replacement therapy sometimes experience increased blood pressure. Blood pressure should be monitored with HRT use. Elevation of blood pressure in previously normotensive or hypertensive patients should be investigated and HRT may have to be discontinued.

Ear/Nose/Throat

Otosclerosis
Estrogens should be used with caution in patients with otosclerosis.

Endocrine and Metabolism

Calcium and Phosphorus Metabolism
Because the prolonged use of estrogens with or without progestins influences the metabolism of calcium and phosphorus, estrogens with or without progestins should be used with caution in patients with metabolic and malignant bone diseases associated with hypercalcemia and in patients with renal insufficiency.

Glucose and Lipid Metabolism
A worsening of glucose tolerance and lipid metabolism have been observed in a significant percentage of peri- and postmenopausal patients. Therefore, diabetic patients or those with a predisposition to diabetes should be observed closely to detect any alterations in carbohydrate or lipid metabolism, especially in triglyceride blood levels.

Women with familial hyperlipidemias need special surveillance. Lipid-lowering measures are recommended additionally, before treatment is started. Women with pre-existing hypertriglyceridemia should be followed closely during estrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this condition.

Hypothyroidism
Patients who require thyroid hormone replacement therapy and who are also taking estrogen should have their thyroid function monitored regularly to assure that thyroid hormone levels remain in an acceptable range (see 9.7 Drug-Laboratory Test Interactions).

Other Conditions
Activelle® *LD* contains lactose. In patient with rare hereditary galactose intolerance, lactase deficiency or glucose-galactose malabsorption, the severity of the condition should be taken

into careful consideration before prescribing Activelle® *LD* tablets. The patients should be closely monitored.

Genitourinary

Endometriosis
Symptoms and physical findings associated with a previous diagnosis of endometriosis may reappear or become aggravated with estrogen use.

Uterine Leiomyomata
Pre-existing uterine leiomyomata may increase in size during estrogen use. Growth, pain or tenderness of uterine leiomyomata requires discontinuation of medication and appropriate investigation.

Vaginal Bleeding
Breakthrough bleeding and spotting may occur during the first months of treatment. Abnormal vaginal bleeding, such as breakthrough bleeding or spotting due to its prolongation, irregularity or heaviness, occurring during therapy or continuing after treatment has been discontinued should prompt appropriate diagnostic measures, which may include endometrial biopsy to rule out the possibility of uterine malignancy and the treatment should be re-evaluated.

Hematologic

Venous Thromboembolism
Available epidemiological data indicate that use of estrogen with or without progestin by postmenopausal women is associated with an increased risk of developing venous thromboembolism (VTE).

In the *estrogen plus progestin* arm of the WHI trial, among 10,000 women on combined HRT over a one-year period, there were 18 more cases of VTE, including 8 more cases of pulmonary embolism.[1]

In the *estrogen-alone* arm of the WHI trial, among 10,000 women on estrogen therapy over a one-year period, there were 7 more cases of VTE, although there was no statistically significant difference in the rate of pulmonary embolism.[2]

Generally recognized risk factors for VTE include a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition), severe obesity (body mass index > 30 kg/m^2) and systemic lupus erythematosus. The risk of VTE also increases with age and smoking.

The risk of VTE may be temporarily increased with prolonged immobilization, major surgery or trauma. In women on HRT, attention should be given to prophylactic measures to prevent VTE following surgery. Also, patients with varicose veins should be closely supervised. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, hormone therapy should be discontinued immediately, given the risks of long-term disability or fatality.

If feasible, estrogens with or without progestins should be discontinued at least 4-6 weeks before major surgery which may be associated with an increased risk of thromboembolism such as abdominal or orthopaedic surgery to lower limbs, or during periods of prolonged immobilization. Treatment should not be restarted until the woman is completely mobilised.

Hepatic/Biliary/Pancreatic

Gallbladder Disease
A 2 to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens has been reported.

Hepatic Hemangioma
Particular caution is indicated in woman with hepatic hemangiomas as estrogen may cause an exacerbation of this condition.

Jaundice
Caution is advised in patients with a history of liver and/or biliary disorders. If cholestatic jaundice develops during treatment, the treatment should be discontinued and appropriate investigations carried out.

Liver Function Tests
Liver function tests should be done periodically in subjects who are suspected of having hepatic disease. For information on endocrine and liver function tests, see **Monitoring and Laboratory Tests**.

Liver Disorders
Patients who have or have previously had liver disorder such as liver adenoma should be closely supervised as this condition may recur or be aggravated during treatment with Activelle® *LD*.

Immune
Angioedema
Estrogen may induce or exacerbate symptoms of angioedema, in particular in woman with hereditary angioedema.

Systemic Lupus Erythematosus
Particular caution is indicated in women with systemic lupus erythematosus, as HRT may cause an exacerbation of this condition.

Monitoring and Laboratory Tests
Before Activelle® *LD* is administered, the patient should have a complete physical examination including a blood pressure determination. Breasts and pelvic organs should be appropriately examined and a Papanicolaou smear should be performed. Endometrial biopsy should be done only when indicated. Baseline tests should include mammography, measurements of blood glucose, calcium, triglycerides and cholesterol, and liver function tests.

The first follow-up examination should be done within 3-6 months after initiation of treatment to assess response to treatment. Thereafter, examinations should be made at intervals at least once a year. Appropriate investigations should be arranged at regular intervals as determined by the physician.

The importance of regular self-examination of the breasts should be discussed with the patient.

Neurologic

Cerebrovascular Insufficiency
Patients who develop visual disturbances, classical migraine, transient aphasia, paralysis or loss of consciousness should discontinue medication.

Patients with a previous history of classical migraine and who develop a recurrence or worsening of migraine symptoms should be re-evaluated.

Dementia
Available epidemiological data indicate that the use of combined *estrogen plus progestin* in women age 65 and over may increase the risk of developing probable dementia.

The Women's Health Initiative Memory Study (WHIMS), a clinical substudy of the WHI, was designed to assess whether postmenopausal hormone replacement therapy (oral *estrogen plus progestin* or oral *estrogen-alone*) reduces the risk of dementia in women aged 65 and over (age range 65-79 years) and free of dementia at baseline.[6,7]

In the *estrogen plus progestin* arm of the WHIMS (n=4532), women with intact uteri were treated with daily 0.625 mg conjugated equine estrogens (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) or placebo for an average of 4.05 years. The results, when extrapolated to 10,000 women treated over a one-year period showed:

- 23 more cases of probable dementia (45 on combined HRT versus 22 on placebo).[6]

In the *estrogen-alone* arm of the WHIMS (n=2947), women with prior hysterectomy were treated with daily 0.625 mg CEE or placebo for an average of 5.21 years. The results, when extrapolated to 10,000 women treated over a one-year period showed:

- 12 more cases of probable dementia (37 on *estrogen-alone* versus 25 on placebo), although this difference did not reach statistical significance.[7]

When data from the *estrogen plus progestin* arm of the WHIMS and the *estrogen-alone* arm of the WHIMS were combined, as per the original WHIMS protocol, in 10,000 women over a one-year period, there were:

- 18 more cases of probable dementia (41 on *estrogen plus progestin* or *estrogen-alone* versus 23 on placebo).[7]

Epilepsy
Particular caution is indicated in women with epilepsy, as estrogens with or without progestins may cause an exacerbation of this condition.

Ophthalmologic
See 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS **- Neurologic.**

Renal

Fluid Retention
Estrogens with or without progestins may cause fluid retention. Therefore, particular caution is indicated in cardiac or renal dysfunction or asthma. If, in any of the above-mentioned conditions, a worsening of the underlying disease is diagnosed or suspected during treatment, the benefits and risks of treatment should be re-assessed based on the individual case.

Reproductive Health
See 7.1 Special Populations.

7.1 Special Populations

7.1.1 Pregnant Women

Activelle® *LD* is contraindicated during pregnancy.

If pregnancy occurs during medication with Activelle® *LD* tablets, treatment should be withdrawn immediately.

Data on a limited number of exposed pregnancies indicate adverse effects of norethindrone on the fetus. At doses higher than normally used in Oral Contraceptives (OC) and HRT formulations masculinisation of female fetuses was observed.

The results of most epidemiological studies to date relevant to inadvertent fetal exposure to combinations of estrogens and progestins indicate no teratogenic or fetotoxic effect.

7.1.2 Breast-feeding

Activelle® *LD* is contraindicated when breastfeeding.

7.1.3 Pediatrics

Activelle® *LD* tablets are not indicated for use in a pediatric population. Safety and effectiveness in pediatric patients have not been established.

7.1.4 Geriatrics

Geriatrics (> *65* years of age): Experience in treating women older than 65 years is limited.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

See 7 WARNINGS AND PRECAUTIONS regarding potential induction of malignant neoplasms and adverse effects similar to those of oral contraceptives.

The following adverse reactions have been reported with estrogen/progestin combination in general:

Blood and Lymphatic System Disorders
Altered coagulation tests (see 7 WARNINGS AND PRECAUTIONS, 9.7 Drug-Laboratory Test Interactions)

Cardiac Disorders

Palpitations; increase in blood pressure (see 7 WARNINGS AND PRECAUTIONS); coronary thrombosis

Endocrine Disorders
Increased blood sugar levels; decreased glucose tolerance

Eye Disorders
Neuro-ocular lesions (e.g. retinal thrombosis, optic neuritis); visual disturbances; steepening of the corneal curvature; intolerance to contact lenses

Gastrointestinal Disorders
Nausea; vomiting; abdominal discomfort (cramps, pressure, pain, bloating)

General Disorders and Administration Site Conditions
Fatigue; changes in appetite; changes in body weight; change in libido

Hepatobiliary Disorders
Gallbladder disorder; asymptomatic impaired liver function; cholestatic jaundice

Musculoskeletal and Connective Tissue Disorders
Musculoskeletal pain including leg pain not related to thromboembolic disease (usually transient, lasting 3-6 weeks) may occur

Nervous System Disorders
Aggravation of migraine episodes; headaches; dizziness; neuritis

Psychiatric Disorders
Mental depression; nervousness; irritability

Renal and Urinary Disorders
Cystitis; dysuria; sodium retention; edema

Reproductive System and Breast Disorders
Breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; vaginal itching/discharge; dyspareunia; endometrial hyperplasia; pre-menstrual-like syndrome; reactivation of endometriosis; changes in cervical erosion and amount of cervical secretion; breast swelling and tenderness

Skin and Subcutaneous Tissue Disorders
Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism and acne

Vascular Disorders
Isolated cases of: thrombophlebitis; thromboembolic disorders

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

Adverse events reported by investigators in the Activelle® *LD* pivotal trial at a frequency of ≥1% are shown in Table 1 below. The regimens evaluated Activelle® *LD* over a 6-month treatment period.

Table 1: Treatment-Emergent Adverse Events with Possible or Probable Relationship Reported at a Frequency of ≥ 1% with Activelle® *LD*

	Activelle® *LD* (n=194)	Placebo (n=200)
Gastrointestinal disorder		
Nausea	3%	2%
Dyspepsia	2%	-[1]
Abdominal distension	1%	-[1]
Abdominal pain	1%	2%
Diarrhea	1%	-[1]
Musculoskeletal and connective tissue		
Back pain	1%	-[1]
Nervous System		
Headache	11%	8%
Dizziness	1%	-[1]
Vascular disorder		
Vaginal hemorrhage	25%	12%
Hot flush	2%	3%
Urogenital/Reproductive System		
Endometrial thickening	9%	4%
Uterine leiomyoma	3%	2%
Ovarian cyst	2%	-[1]
Vaginal discharge	1%	-[1]
Breast pain	1%	-[1]
Vulvovaginal mycotic infection	1%	-[1]
Uterine polyp	1%	-[1]

1. No adverse events reported

The most frequently reported adverse events in the clinical trials with Activelle® *LD* tablets were vaginal hemorrhage (any release of blood from uterus), endometrial thickening (double layer measured at ≥ 5 mm) and headache. The majority of AEs occurred with similar frequency in the treatment groups and were classified as mild or moderate in severity. As

expected, the incidence of vaginal bleeding was higher in the continuous combined treatment groups Activelle® *LD* (25%) than in the placebo group (12%).

There were no reports of thromboembolic events in any treatment group. Clinically important symptoms related to the breast (breast discomfort, breast pain and tenderness) were reported by < 2% of subjects treated with the Activelle® *LD* regimens, which was comparable with the placebo group.

8.3 Less Common Clinical Trial Adverse Reactions

Cardiac Disorders: Chest discomfort; chest pain

Gastrointestinal: Abdominal pain upper; constipation; epigastric discomfort; gastritis; stomach discomfort

General and Administration Site Conditions: Malaise; suprapubic pain

Infections and Infestations: Salpingitis; vaginal candidiasis

Musculoskeletal, Connective Tissue and Bone: Musculoskeletal stiffness; neck pain; pain in extremity

Nervous System Disorders: Migraine; disturbance in attention; mental impairment; restless legs syndrome; stress incontinence

Other: Post procedural hemorrhage; liver function test abnormal

Renal and Urinary Disorders: Fluid retention; urinary retention

Reproductive System and Breast: Breast tenderness; breast discomfort; vulvovaginal dryness; cervical cyst

Respiratory, Thoracic and Mediastinal Disorders: Epistaxis

Skin and Subcutaneous Tissue Disorders: Pruritus genital; acne; skin irritation

Vascular Disorders: Hypertension; varicose vein

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

None of the observed changes with regard to hematology and clinical chemistry in clinical studies of Activelle® *LD* were clinically relevant.

8.5 Post-Market Adverse Reactions

The adverse events presented below have been reported by women taking Activelle® *LD* or a higher estradiol/norethindrone acetate formulation (Activelle® 1 mg/0.5 mg). They have been spontaneously reported and are, by an overall judgment, considered possibly related to treatment.

Cardiac Disorders: Myocardial infarction

Eye Disorders: Visual disturbances

Gastrointestinal Disorders: Dyspepsia, vomiting

Hepatobiliary Disorders: Gallbladder disease, gallstones, cholelithiasis, cholelithiasis aggravated, cholelithiasis recurrence

Immune System Disorders: Generalized hypersensitivity reactions (e.g. anaphylactic reaction/shock)

Musculoskeletal and Connective Tissue Disorders: Leg cramps

Neoplasm Benign and Malignant: Endometrial cancer, uterine fibroid

Nervous System Disorders: Dizziness, stroke

Other: Weight decreased, blood pressure increased

Psychiatric Disorders: Insomnia, anxiety, libido decreased, libido increased

Reproductive System and Breast Disorders: Endometrial hyperplasia, vulvovaginal pruritus

Skin and Subcutaneous Tissue Disorders: Seborrhea, rash, angioneurotic edema, vascular purpura

Vascular Disorders: Hypertension aggravated

If adverse symptoms persist, the prescription of HRT should be re-considered.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Estrogens are partially metabolized by cytochrome P450 3A4 (CYP3A4) as shown *in vitro* and *in vivo* studies. Therefore, estrogen drug metabolism may be affected by inducers or inhibitors of CYP3A4.

9.3 Drug-Behavioural Interactions

None identified.

9.4 Drug-Drug Interactions

Table 2: Established or Potential Drug-Drug Interactions

Drug Class	Effect	Clinical comment
Anticonvulsants (e.g. phenobarbital, hydantoin, phenytoin, carbamazepine)	Reduce plasma concentrations of estrogens	Therapeutic monitoring is recommended

Drug Class	Effect	Clinical comment
Anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz)	Reduce plasma concentrations of estrogens	Therapeutic monitoring is recommended
Protease inhibitors (e.g. ritonavir, telaprevir, nelfinavir)	Reduce plasma concentrations of estrogens	Therapeutic monitoring is recommended
Imidazoles (e.g. ketoconazole)	Increase plasma concentration of estrogens	Therapeutic monitoring is recommended
Barbiturates	Induce liver enzymes, may interfere with activity of orally administered estrogens	Therapeutic monitoring is recommended
Anticoagulants	Estrogens may diminish effectiveness	Therapeutic monitoring is recommended
Antidiabetics	Estrogens may diminish effectiveness	Therapeutic monitoring is recommended
Antihypertensives	Estrogens may diminish effectiveness	Therapeutic monitoring is recommended

9.5 Drug-Food Interactions

Grapefruit juice may increase plasma concentrations of estrogen.

9.6 Drug-Herb Interactions

It was found that some herbal products (e.g. St. John's Wort) which are available as over-the-counter (OTC) products might interfere with steroid metabolism and therefore alter the efficacy and safety of estrogen/progestin products.

Physicians and other health care providers should be made aware of other non-prescription products concomitantly used by the patient, including herbal and natural products obtained from the widely spread health stores.

9.7 Drug-Laboratory Test Interactions

The results of certain endocrine and liver function tests may be affected by estrogen-containing products:

- increased prothrombin time and partial thromboplastin time; increased levels of fibrinogen and fibrinogen activity; increased coagulation factors VII, VIII, IX, X; increased norepinephrine-induced platelet aggregability; decreased antithrombin III;

- increased thyroxine-binding globulin (TBG), leading to increased circulating total thyroid hormone (T4) as measured by column or radioimmunoassay; T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered;
- other binding proteins may be elevated in serum i.e., corticosteroid binding globulin (CBG), sex-hormone binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively; free or biologically active hormone concentrations are unchanged;
- impaired glucose tolerance;
- increased serum triglycerides and phospholipids concentration.

The results of the above laboratory tests should not be considered reliable unless therapy has been discontinued for 2-4 weeks.

The pathologist should be informed that the patient is receiving HRT when relevant specimens are submitted.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Estradiol: The active ingredient, synthetic estradiol, is chemically and biologically identical to endogenous human estradiol.

Estradiol, E2, is the major estrogenic hormone secreted by the human ovary. Among numerous effects, E2 is responsible for the development and maintenance of the female reproductive system and of secondary sexual characteristics. It promotes growth and development of the vagina, uterus, fallopian tubes and breasts. E2 contributes to the shaping of the skeleton, to the maintenance of tone and elasticity of urogenital structures, to changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, to the growth of auxiliary and pubic hair, and to the pigmentation of the nipples and genitals. It also affects the release of pituitary gonadotropins.

After menopause, when the ovaries have ceased to function, only small amounts of E2 are still produced. E2 is produced in the body by the aromatisation of androstenedione to estrone, E1, and to a lesser extent, testosterone to estradiol. Estrone is transformed to estradiol by the enzyme 17ß-hydroxysteroid-dehydrogenase. Both enzymes prevail in fat, liver and muscle tissue.

Loss of ovarian E2 production after menopause can result in instability of thermoregulation causing hot flushes associated with sleep disturbance and excessive sweating; accelerated loss of bone matrix and mineral, resulting in osteoporosis; alterations in lipid metabolism and urogenital atrophy, causing dyspareunia and urinary incontinence.

Norethindrone acetate: Because estrogens promote the growth of the endometrium, unopposed estrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestin may reduce the estrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Norethindrone acetate, NETA, is a potent progestin that essentially mimics the biological effects of progesterone. Tissue effects of NETA are dependent on prior estrogen stimulation, and progesterone receptors have been identified in all tissues containing estrogen receptors.

NETA induces protein synthesis and also reduces the number of estrogen and progesterone receptors, thereby limiting excessive growth stimulation of target tissues by estrogen. 17-hydroxysteroid-dehydrogenase, which locally oxidizes E2 to its weaker estrogenic metabolite estrone, is also produced by NETA.

One of the major targets of NETA is the uterus, where it induces secretory transformation of the estrogen-primed endometrium. Once transformation of the endometrium is completed, the estrogen-primed endometrium is shed resulting in a regular cyclical bleeding.

Continuous addition of NETA in addition to estradiol will result in maintenance of the endometrium in an atrophic state in most of the women. This regimen avoids monthly withdrawal bleeding.

10.2 Pharmacodynamics

Estrogen pharmacology
Estradiol, E_2, is chemically and biologically identical to the endogenous human hormone. It is the major estrogenic hormone secreted by the human ovary which is also produced in small quantities (<20 pg/mL) in the postmenopausal woman. Among numerous effects, E_2, is responsible for the development and maintenance of the female reproductive system and secondary sex characteristics. By a direct action, it causes growth and development of the uterus, fallopian tubes, and vagina. With other hormones, such as pituitary hormones and progesterone, it causes enlargement of the breasts through promotion of ductal growth, stromal development, and the accretion of fat.

E_2 is intricately involved with other hormones, especially progesterone, in the processes of the ovulatory menstrual cycle and pregnancy and affect the release of pituitary gonadotropins. It also contributes to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bone that allow for the pubertal growth spurt and its termination, and pigmentation of the nipples and genitals.

Estrogen replacement therapy acts through a negative feedback pathway to reduce elevated circulating levels of luteinizing hormone (LH) and follicule-stimulating hormone (FSH) observed in postmenopausal women.

Progestin pharmacology
Norethindrone Acetate, NETA, is a progestin that essentially mimics the biological effects of progesterone. NETA enhances cellular differentiation and generally opposes the actions of estrogen, by decreasing estrogen receptor levels, increasing local metabolism of estrogen to less active metabolites, or by inducing gene products that blunt cellular responses to estrogen.

NETA exerts its effect in target cells by binding to specific progesterone receptors which interact with progesterone response elements in target genes. Progesterone receptors have been identified in the female reproductive tract, breast, pituitary, hypothalamus and central nervous system. NETA produces similar endometrial changes to those of the naturally occurring hormone progesterone.

Unopposed estrogen therapy in women with intact uteri is associated with an increased risk of endometrial hyperplasia and endometrial carcinoma. The concomitant use of an appropriate

dose of a progestogen for an adequate time period reduces the incidence of endometrial hyperplasia and carcinoma in women with intact uteri who are receiving estrogen replacement therapy.

10.3 Pharmacokinetics

Table 3: Pharmacokinetic Parameters after Administration of 2 Tablets of Activelle® *LD* to Healthy Postmenopausal Women

	2 x Activelle® LD (n=24) Mean[1] (%CV)[2]
Estradiol[3] (E_2)	
AUC_{0-t} (pg/mL*h)	697.3 (53)
C_{max} (pg/mL)	26.5 (37)
t_{max} (h): median (range)	6.5 (0.5-16.0)
$t_{1/2}$ (h)[4]	14.5[5] (27)
Estrone[3] (E_1)	
AUC_{0-t} (pg/mL*h)	4469.1 (48)
C_{max} (pg/mL)	195.5 (37)
t_{max} (h): median (range)	6.0 (1.0 -9.0)
$t_{1/2}$ (h)[4]	10.7 (44)[6]
Norethindrone (NET)	
AUC_{0-t} (pg/mL*h)	8407.2 (43)
C_{max} (pg/mL)	2375.4 (41)
t_{max} (h): median (range)	0.8 (0.7-1.3)
$t_{1/2}$ (h)	11.4 (36) [7]

AUC = area under the curve, 0 – last quantifiable sample
C_{max} = maximum plasma concentration,
t_{max} = time at maximum plasma concentration,
$t_{1/2}$ = half-life,

1. geometric mean;
2. geometric % coefficient of variation;
3. baseline unadjusted data;
4. baseline adjusted data ;
5. n=16;
6. n=13;
7. n=21

Absorption
Following oral administration of Activelle® *LD* tablets, estradiol in micronized form, rapid absorption from the gastrointestinal tract occurs. The half-life of estradiol is about 15 hours. It circulates bound to sex hormone binding globulin (SHBG) (37%) and to albumin (61%), while only approximately 1-2% is unbound.

Distribution
After oral administration of an Activelle® *LD* tablet, norethindrone acetate is rapidly absorbed and transformed to norethindrone (NET). The terminal half-life of NET is about 9-11 hours. NET binds to SHBG (36%) and to albumin (61%).

Metabolism
After rapid absorption from the gastrointestinal tract, estradiol undergoes a first-pass metabolism in the liver and other enteric organs, and reaches a peak plasma concentration of

approximately 24 pg/mL (CV 38 %) (after administration of two Activelle® *LD* tablets) within 5-8 hours.

Metabolism of estradiol, occurs mainly in the liver and the gut but also in target organs, and involves the formation of less active or inactive metabolites, including estrone, catecholestrogens and several estrogen sulfates and glucuronides. Estrogens are excreted with the bile, hydrolysed and reabsorbed (enterohepatic circulation), and mainly eliminated in urine in biologically inactive form.

Elimination
After absorption, norethindrone undergoes first-pass metabolism in the liver and other enteric organs, and reaches a peak plasma concentration of approximately 2.4 ng/mL (CV 41 %) (after administration of two Activelle® *LD* tablets) within 0.5-1.5 hours. The most important metabolites of norethindrone are isomers of 5α-dihydro-NET and of tetrahydro-NET, which are excreted mainly in the urine as sulfate or glucuronide conjugates.

The pharmacokinetics of estradiol are not influenced by NET.

Special Populations and Conditions

- **Pediatrics:** Activelle® *LD* tablets are not indicated for use in a pediatric population. Safety and effectiveness in pediatric patients have not been established.
- **Geriatrics:** Experience in treating women older than 65 years is limited. The pharmacokinetics in the elderly has not been studied.
- **Sex:** Activelle® *LD* tablets are not indicated for use in a male population.
- **Genetic Polymorphism:** No specific information available.
- **Ethnic Origin:** No specific information available.
- **Hepatic Insufficiency:** No specific information available.
- **Renal Insufficiency:** No specific information available.

11 STORAGE, STABILITY AND DISPOSAL

Keep out of reach of children. Store in a dry place, protected from light. Store between 15-25° C. Do not refrigerate.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

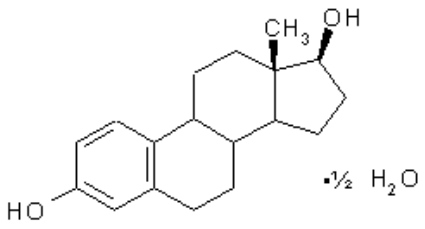
Drug Substance: Estradiol

Non-proprietary name of the drug product: Estradiol USP

Chemical name: 1. Estra-1, 3, 5 (10)-triene, 3, 17ß-diol

Molecular formula and molecular mass: $C_{18}H_{24}O_2$
272.39

Structural formula:



Physicochemical properties:

Description: White or almost white crystalline powder

Solubility: Practically insoluble in water. 5.0×10^{-3} g/L

Melting point: 173 - 179°C

pKa: 10.71

n-octanol/water partition coefficient: log P_{OW} =3.30

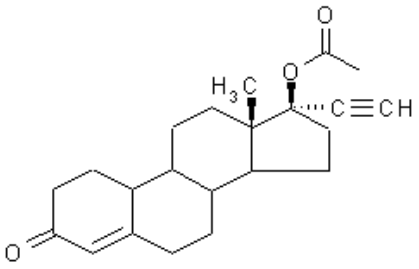
Drug Substance: Norethindrone acetate

Non-proprietary name of the drug product: Norethindrone acetate USP

Chemical name:
1. 19-Norpregn-4-en-20-yn-3-one, 17-(acetyloxy)-, (17α)
2. 17-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one acetate

Molecular formula and molecular mass: C22H28O3
340.5

Structural formula:



Physicochemical properties:

Description:	White to yellowish-white crystalline powder
Solubility:	Practically insoluble (USP definition) in water
Melting point:	161 - 162°C
pKa:	The highest pKa value of NETA protonated at the conjugated ketone group in position 3 was calculated as -5, and the lowest pKa value of the neutral molecule was calculated as 19.

n-octanol/water partition coefficient: log P_{OW} = 3.67.

14 CLINICAL TRIALS

Activelle® *LD* is a low dose continuous combined hormone replacement therapy (HRT) for use in postmenopausal women. Activelle® *LD* was designed to use the minimum effective dose combination of estradiol (E2) and norethindrone acetate NETA for relief of vasomotor symptoms and endometrial protection. Activelle® *LD* contains 0.5 mg of estradiol (E2) and 0.1 mg norethindrone acetate (NETA).

14.1 Clinical Trials by Indication

Effects on Menopausal Symptoms

Study demographics and trial design

A pivotal study, ALD-1537**,** was designed to identify the optimal NETA dose (0.1 mg or 0.25 mg) to be used in combination with 0.5 mg E2. This was a six month double-blind, randomised, parallel-group, placebo-controlled trial that comprised a 2-3 week screening period to assess baseline menopausal symptoms, followed by 24 weeks of treatment. The trial population was postmenopausal women with an intact uterus, target age 46-65 years, with a minimum of seven moderate to severe hot flushes per day or 50 per week. A total of 575 healthy postmenopausal women were randomized to receive Activelle® *LD* or placebo: 194 to Activelle® *LD*, 182 to 0.5 mg E2 + 0.25 mg NETA, and 201 to placebo. The subjects' mean age was 55.5 years (range 44-65 years).

Supportive data for the choice of the E2 and NETA doses used in Activelle® *LD* were provided by clinical trials.

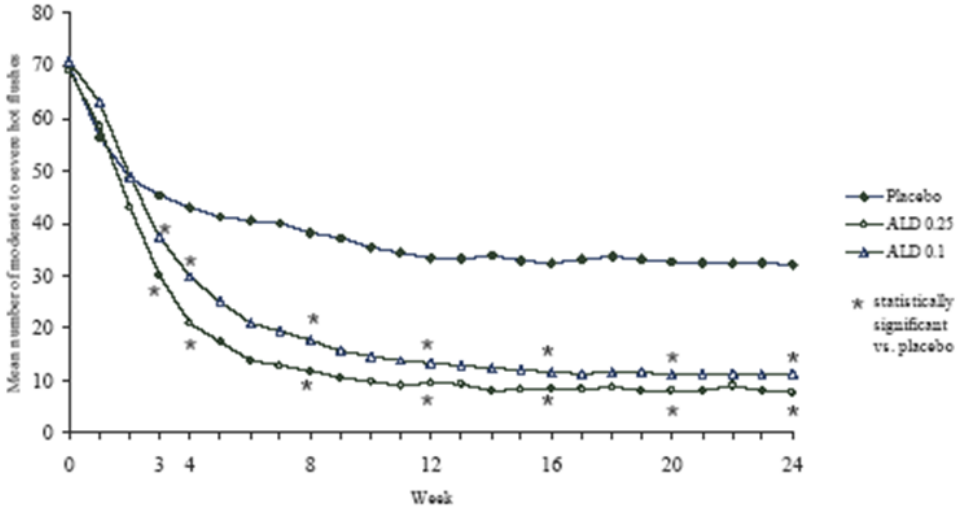
Table 4: Study Population and Subject Disposition: Studies of Effects on Vasomotor Symptoms

Study	ALD-1537
Number of subjects randomised	577
Demographic details	
Age (years)	
mean	55.5
(range)	(44-65)
Race	
White (%)	95
Black (%)	0
Asian/Pacific Islander (%)	1
Not available (%)	4
Other (%)	0
Key criteria for inclusion	
Months since spontaneous amenorrhoea	I: 12 or more months II: 6 or more months III unknown
FSH (mIU/mL)	I not specified II & III >40
E2 (pg/mL)	I not specified II & III <25
Intact uterus	Yes
Endometrial thickness (mm)	<5.0
Minimum moderate to severe hot flushes	
per day	7
per week	50
Disposition	
Number (%) patients	
Treated	575 (99%)
Completed study	508 (88%)
Withdrawn	67 (12%)
Reasons for withdrawal (n, %)	
Adverse event	31 (5%)
Ineffective therapy	21 (4%)
Protocol non-compliance	8 (1%)
Other reason	9 (2%)

Study results

In the pivotal study of Activelle® *LD*, the primary efficacy endpoint was the mean change in the number of moderate to severe hot flushes per week from baseline to week 8 and the mean change in severity score of moderate to severe hot flushes from baseline. The severity score was defined as SS1 = (2x number of moderate hot flushes + 3x number of severe hot flushes)/(number of moderate + number of severe hot flushes).

Compared to placebo, Activelle® *LD* treatments significantly reduced the number of moderate to severe hot flushes beginning at treatment week 3 (Figure 1). The change from baseline in the number of moderate to severe hot flushes per week in the Activelle® *LD* and formulation containing 0.5 mg E2 + 0.25 mg NETA groups were significantly different from placebo ($p \leq 0.001$) at weeks 3 through 24, however the two active groups were not significantly different from each other.



*ALD 0.25 is not approved for use in Canada
** ALD 0.1 = Activelle® *LD*

Figure 1: Mean Number of Moderate to Severe Hot Flushes by Week (Study ALD-1537, ITT Population)

Following Activelle® *LD* treatment, there was a decrease in the severity score of moderate to severe hot flushes with a mean change of -9.1 in the Activelle® *LD* group by week 8. In the placebo group a slight and more gradual decrease was seen, with a mean change of -3.4 by week 8.

The reduction in hot flush severity score was statistically significant when comparing Activelle® *LD* with placebo from week 3 to week 24 (p=0.001).

The treatment differences at week 4 were -1.3 (CI -2.1; -0.7) for Activelle® *LD* compared with placebo; at week 8 they were -5.1 (CI -7.1; -3.4) for Activelle® *LD* compared with placebo, and at week 12 they were -6.1 (CI -8.6; -4.2) for Activelle® *LD* compared with placebo.

A weekly weighted hot flush score which was a composite score incorporating the weekly number of hot flushes and the severity of each hot flush was also assessed. The weekly weighted hot flush score was calculated by multiplying the number of mild hot flushes by a factor of one, the number of moderate hot flushes by a factor of two, and the number of severe hot flushes by a factor of three, and then adding these scores on a weekly basis.

Following Activelle® *LD* treatment, there was a decline in the Hot Flush Weekly Weighted Score (HFWWS), from a mean score of 185.8 to 48.2 in the Activelle® *LD* group at week 8. In the placebo group, a slight and more gradual decrease in the HFWWS was seen, from a

mean score of 183.5 at baseline to 101.1 at week 8. A statistically significant treatment difference ($p < 0.001$) was seen for all time points when comparing Activelle® *LD* with placebo.

Other efficacy endpoints assessed in this study were: responder analysis, Greene Climacteric Scale, urogenital symptom score.

Responders were defined as subjects with at least a 90% improvement in HFWWS from baseline. Analysis of the percentage of responders in the pivotal ALD study showed a statistically significant treatment effect at weeks 4, 8, 12 and 24 (all $p = 0.001$; Table 5).

Table 5: Percentage of Responders (Pivotal ALD Study: ITT Population)

	ALD 0.1		**Placebo**	
Week	% Responders	CI	% Responders	CI
4	21[1]	15, 27	10	5, 14
8	44[1]	37, 51	13	8, 17
12	56[1]	49, 63	20	14, 25
24	66[1]	59, 73	23	17, 28

1. statistically significant compared to placebo (p=0.001)

The Greene Climacteric Scale was assessed at Visits 2 to 6. The Greene Climacteric Scale comprises 21 symptoms in three groups (Psychological Factors, Somatic Factors, Vasomotor Factors) with a separate question regarding sexual interest. Greene Climacteric Scale mean total symptom scores decreased during the treatment period, with Activelle® *LD* mean values dropping from 18.0 at baseline to 8.0 at week 8. There was a smaller reduction in score in the placebo group, from 17.7 to 12.2. There was a statistically significant treatment difference ($p = 0.001$) for all time points when comparing Activelle® *LD* with placebo.

Most of the subjects in the pivotal ALD study experienced mild urogenital symptoms at baseline such that the mean urogenital symptom score was below 1 at week 0 in all treatment groups. Changes in the urogenital symptom score could not achieve statistical significance.

Laboratory investigations were carried out in a subset of 157 women from trial ALD-1537, for 24 weeks, to examine lipid, hemostasis parameters and glucose metabolism parameters. Routine hematology and biochemistry evaluations were performed on blood samples taken during the course of trial ALD-1537, involving 575 women over 24 weeks.

No clinically significant results were observed.

15 MICROBIOLOGY

Not applicable.

16 NON-CLINICAL TOXICOLOGY

Due to physiological, pharmacokinetic and pharmacodynamic interspecies differences, quantitative extrapolation from animals to humans must be carried out with great caution. There is an extensive clinical experience with the use of E2 and NETA in humans and no effects can be predicted from animal toxicology findings other than those documented with human use.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrActivelle® LD

Estradiol and Norethindrone Acetate Tablets

Read this carefully before you start taking **Activelle® LD** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Activelle® LD**.

Serious Warnings and Precautions

In postmenopausal women taking estrogen-alone, who had surgery to remove the uterus (called a hysterectomy), there is an increased risk of:

- stroke (bleeding or blot clot in the brain), and
- deep vein thrombosis (blood clots in the deep veins of the leg or arm).

Estrogens with progestin, like Activelle® LD, should:

- not be used to prevent heart disease or stroke.
- be used at the **lowest effective dose** and for the **shortest period of time** possible. You should have regular medical check-ups.

What is Activelle® LD used for?

Activelle® LD is used only in women who still have a uterus. It is used to treat the following condition that can occur as a result of lower estrogen levels associated with menopause:

- moderate to severe vasomotor symptoms of menopause (such as hot flashes).

How does Activelle® LD work?

After menopause, your body makes less of the estrogen.

Activelle® LD is a Hormone Replacement Therapy (HRT) that contains 2 ingredients that have different functions. The estradiol (a type of estrogen) in Activelle® LD replaces the estrogen that some women are missing. This may help relieve your menopausal symptoms such as hot flashes. Since estrogen may also stimulate the lining of the uterus to grow Activelle® LD also contains the progestin hormone called norethindrone acetate (NETA). NETA helps to reduce the risk of overgrowth of the lining of the uterus (a condition called endometrial hyperplasia), which could lead to cancer of the lining of the uterus (womb).

What are the ingredients in Activelle® LD?

Medicinal ingredients: Estradiol and norethindrone acetate.

Non-medicinal ingredients: Hydroxypropylcellulose, hypromellose, lactose monohydrate, magnesium stearate, maize starch, talc and triacetin

Activelle® *LD* comes in the following dosage forms:

Film-coated tablets: 0.5 mg estradiol (as estradiol hemihydrate) and 0.1 mg norethindrone acetate

Do not use Activelle® LD if:

- you are allergic to estradiol, norethindrone acetate or to any of the ingredients in Activelle® LD
- you have or have had liver problems, and the blood tests to measure how your liver is working have not returned to normal.
- you have or have had estrogen-dependent or progestin-dependent cancer (e.g. endometrial cancer).
- you have thickening of the lining of the uterus (endometrial hyperplasia).
- you have or have had breast cancer.
- you have unexpected or unusual vaginal bleeding.
- you are pregnant or think you might be pregnant.
- you are breast-feeding
- you have, or have had a heart attack, stroke, angina or heart disease
- you have or have had blood clotting problems such as:
    - deep vein thrombosis (where a blood clot forms in a deep vein);
    - pulmonary embolism (where a blood clot forms in the lung);
    - thromboembolism (where a blood clot blocks the flow of blood through your veins).
- you have partial or complete loss of vision due to blood vessel disease of the eye (called ophthalmic vascular disease)
- you have porphyria (a disease caused by how your body makes heme – a component of your blood).
- you have migraine headaches.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Activelle® LD. Talk about any health conditions or problems you may have, including if you:

- have a history of allergy or intolerance to any medications or other substances.
- have a personal history of breast disease (including breast lumps) and/or breast biopsies, or a family history of breast cancer.
- have experienced any unusual or undiagnosed vaginal bleeding.
- have or had:
    - a history of uterine fibroids (growths) inside of your uterus;
    - endometriosis (growth of the uterine lining outside your uterus); and/or
    - a history of overgrowth of the lining of the uterus (endometrial hyperplasia)
- have a history of liver disease or liver tumors, jaundice (yellowing of the eyes and/or skin).
- have a history of itching related to estrogen use or during pregnancy.
- have a history of migraine headaches.
- have a history of high blood pressure.

- have a personal or family history of blood clots, or a personal history of heart disease or stroke.
- have a history of kidney disease.
- have asthma.
- have seizures (epilepsy).
- have gallbladder disease.
- have a history of bone disease (this includes certain metabolic conditions or cancers that can affect the calcium and phosphorus levels in your blood).
- have a condition where your thyroid gland fails to produce enough thyroid hormone (hypothyroidism) and you are being treated with thyroid hormone replacement therapy.
- have a condition called hereditary angioedema, or if you have had episodes of rapid swelling of the hands, feet, face, lips, eyes, tongue, throat (airway blockage) or digestive tract.
- have been diagnosed with lupus.
- have been diagnosed with diabetes.
- have or had high levels of fat in your blood (cholesterol, triglycerides).
- have been diagnosed with depression.
- will have to lie in bed for an extended period of time (prolonged bed rest).
- are pregnant or may be pregnant.
- are breastfeeding.
- have been diagnosed with hearing loss due to abnormal bone growth in your ear (otosclerosis).
- have an intolerance to lactose. Activelle® LD contains lactose.
- have eye problems.
- smoke.
- are having surgery.

Other warnings you should know about:

Breast cancer:

- There is a higher risk of breast cancer in postmenopausal women taking combined estrogen plus progestin.
- Estrogens with or without progestins should not be taken by women who have a personal history of breast cancer.
- Talk to your healthcare professional before starting HRT if you have:
    - a family history of breast cancer or breast lumps, breast biopsies or abnormal mammograms (breast x-rays)
    - never had a baby before or had your first full-term pregnancy at an older age
    - you are overweight
    - you started menstruating at an early age

Overgrowth of the lining of the uterus and cancer of the uterus:

- Taking estrogen-only therapy by postmenopausal women who still have a uterus increases your risk of excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the lining of the womb (endometrial cancer).

- Talk to your healthcare professional about progestin therapy and risk factors for endometrial hyperplasia and endometrial cancer. You should also report any unexpected or unusual vaginal bleeding to your healthcare professional.

- If you have had your uterus removed, you are not at risk of developing endometrial hyperplasia or endometrial cancer. Progestin therapy is not generally required in women who have had a hysterectomy (surgical removal of the uterus).

Ovarian Cancer: Taking HRT for 5 years or more increases your risk of developing ovarian cancer. Ovarian cancer may develop when using HRT with estrogen alone or estrogen in combination with progestin.

Abnormal Blood Clotting: Taking Activelle® LD can increase your risk of developing blood clots in your large veins. You should discuss risk factors for blood clots with your healthcare professional since blood clots can be life-threatening or cause serious disability. Talk to your healthcare professional if:

- you or a family member has had blood clots.
- you smoke.
- you are overweight.

The risk of blood clots is increased as you get older. It is also temporarily increased:
- if you are inactive for long periods of time.
- following major surgery.

If you are going to have surgery, your healthcare professional may recommend you temporarily stop take Activelle® LD about 4 to 6 weeks before the procedure to reduce the risk of blood clots.

Gallbladder Disease: Your risk of developing gallbladder disease that requires surgery is increased when taking estrogens.

Dementia: Your risk of developing dementia (memory loss) is increased if you are a woman aged 65 and over taking estrogen with progestin.

Check-ups and testing: You will have regular visits with your healthcare professional, before and during your treatment. They will:

- Do a physical exam and blood work (which may include a pregnancy test) before you begin treatment. Your visit may include a blood pressure check, a breast exam, a Pap smear and pelvic exam. You should have a mammogram before starting treatment and at regular intervals as recommended by your healthcare professional.

- Do regular follow-up exams including a breast exam and blood pressure check at least once a year to identify side effects associated with the use of Activelle® LD. Your first follow-up visit should be within 3 to 6 months of starting treatment.

- Advise you to regularly check your own breasts. Talk to your healthcare professional if you are unsure on the technique to use.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Activelle® LD:

- medicines used for the treatment of epilepsy (e.g. phenobarbital, hydantoin, phenytoin and carbamazepine).
- medicines used for tuberculosis (e.g. rifampicin, rifabutin).
- medicines used for the treatment of HIV or hepatitis infections (e.g. nevirapine, efavirenz, ritonavir, telaprevir and nelfinavir).
- medicines used for the prevention or treatment of blood clots (anticoagulant).
- medicines used to treat diabetes.
- medicines used to treat high blood pressure (antihypertensive).
- medicines used to help you relax such as barbiturates.
- herbal treatments to treat depression containing St. John's Wort (Hypericum perforatum).
- medicines used to treat fungal infection such as ketoconazole.
- Grapefruit juice.

How to take Activelle® LD*:*

- You may begin treatment with Activelle® LD on any day of the week that is convenient. If you are switching from another Hormone Replacement Therapy product, start Activelle® LD right after withdrawal bleeding (menstrual period) has ended.
- Your healthcare professional will prescribe the lowest dose to treat your symptoms for as short amount of time as necessary. Speak to your healthcare professional if you think your dose is too strong or not strong enough.
- Activelle® LD is not a contraceptive. If it is less than 12 months since your last menstrual period or you are under 50 years old, you may still need to use additional contraception to prevent pregnancy. Talk to your healthcare professional.

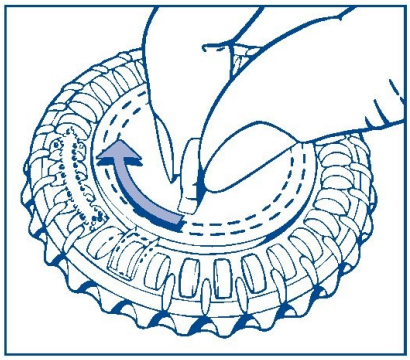
Usual dose:

Take 1 tablet once daily around the same time each day. Once you have finished all the 28 tablets in the pack, start a new pack continuing the treatment without interruption.

How to use the dial pack?
Activelle® LD is supplied in calendar dial-packs of 28 white tablets. Follow the steps below on how to use the calendar dial-pack:

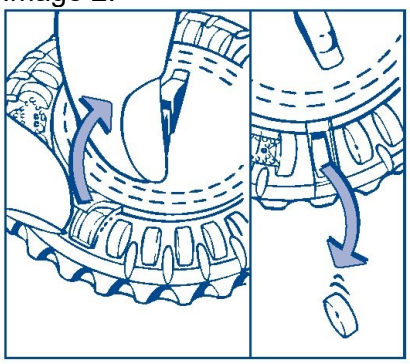
1. **Set the day reminder**
   Turn the inner disc to set the day of the week for the first tablet (see image 1). The day of the week should be aligned with the little plastic tab.

   Image 1:



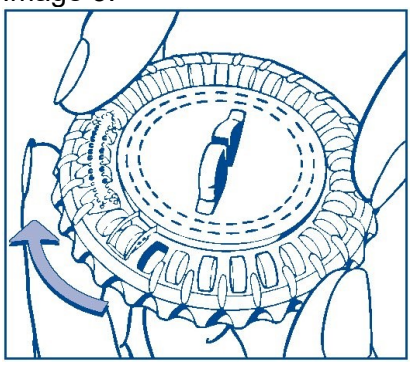
2. **How to take the first tablet**
   The first tablet to be taken is under the sealed opening in the transparent outer rim of the dial-pack. Break the plastic tab and tip out the first tablet (see image 2).

   Image 2:



3. **Following days**
   Move the outer transparent dial clockwise one space to the next day as indicated by the arrow (see image 3). Tip out the next tablet.

   Image 3:



   The transparent dial can only be turned after the tablet in the opening has been removed.

Overdose:

Signs of an overdose may include nausea, vomiting, breast discomfort, fluid retention (swelling), bloating, vaginal bleeding, depressed mood, tiredness, acne, and growth of body or facial hair.

If you think you, or a person you are caring for, have taken too much Activelle® LD, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If you forget to take a tablet and its within 12 hours of the time you should have taken it, take it as soon as you remember. If it has been more than 12 hours do not take this dose. The next dose should be taken at the normal time. Do not take two tablets to make up for the missed dose.

Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting.

What are possible side effects from using Activelle® LD?

These are not all the possible side effects you may have when taking Activelle® LD. If you experience any side effects not listed here, tell your healthcare professional.

- Nausea, vomiting.
- Abdominal cramps, pressure, pain, and bloating.
- Feeling tired (fatigue), inability to sleep or stay awake.
- Changes in appetite, and body weight.
- Change in sex drive.
- Muscle aches and pains, including the legs, abdominal, back, chest, neck, and pelvic.
- Headache, dizziness.
- Anxiety, feeling nervous.
- Vaginal itching, discharge, discomfort, odour.
- Pain during or after sex.
- Breast tenderness, pain, swelling.
- Skin darkening on the face (chloasma)
- Acne, itchy skin.
- Hair loss or abnormal hairiness.
- Diarrhea, constipation.
- Hot flushes.
- Heartburn.
- Loss of focus and thinking.
- Urine leaks.
- Genital dryness.
- Nose bleeds.

Activelle® LD can cause abnormal blood and positive cervical smear test results. Your healthcare professional will decide when to do these tests and will interpret the results.

Serious side effects and what to do about them			
	Talk to your healthcare professional		Stop taking drug and get immediate medical help
Symptom / effect	Only if severe	In all cases	
COMMON			
Peripheral edema: Swelling of arms and legs		✓	
Depression (sad mood that won't go away): difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced libido (sex drive) and thoughts of death or suicide		✓	
Vaginitis: Genital infection with a fungus, vaginal inflammation, discharge, itching, and pain	✓		
UNCOMMON			
Allergic reaction: difficulty swallowing or breathing, wheezing; drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; swelling of the face, lips, tongue or throat.			✓
Erythema multiforme(an allergic skin reaction): raised red or purple skin patches, possibly with blister or crust in the center; possibly swollen lips, mild itching or burning			✓
Erythema nodosum (swelling of the fat cells under the skin): tender red lumps usually on both shins			✓
Vaginal bleeding changes: increased or decreased menstrual bleeding, spotting, infrequent periods or absence of bleeding, severe vaginal bleeding		✓	
Deep Vein Thrombosis (blood clot in the legs or arms): pain or swelling in the leg or arm			✓
Thromboembolism (blood clot in a vein or artery): pain or tenderness or swelling in your arm or leg, skin that is red or warm, coldness, tingling or numbness, pale skin, muscle pain or spasms, weakness			✓
Pulmonary Embolism (blood clot in the lungs): Sharp pain in the chest, coughing up blood, sudden shortness of breath			✓

Serious side effects and what to do about them			
	Talk to your healthcare professional		Stop taking drug and get immediate medical help
Symptom / effect	**Only if severe**	**In all cases**	
Eye disorders: blurred vision, loss of vision in eye, increased sensitivity of the eyes to light, eye pain or redness, swelling and itching of the eyelids, decreased sharpness of vision, eye irritation, blocked eye veins		✓	
Stroke (bleeding or blood clot in the brain): sudden severe headache, vomiting, dizziness, fainting, problems with your vision or speech, weakness or numbness in face, arm or leg			✓
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations.		✓	
Migraine: severe headache often accompanied by nausea, vomiting and sensitivity to light	✓		
RARE			
Breast abnormalities (including breast cancer): dimpling or sinking of the skin, changes in the nipple, or any lumps you see or feel, discharge from breasts, enlarged breasts, swelling			✓
Coronary thrombosis (blocked heart arteries): chest pain and pressure, shortness of breath			✓
Cystitis (bladder infection): increased need to urinate, pain in the pelvis or lower back, frequent urination during the night, cloudy urine that may contain blood, burning sensation when passing urine		✓	
Endometrial hyperplasia (abnormal growth of the lining of the uterus): menstrual bleeding that is heavier or lasts longer than normal, bleeding after menopause, menstrual cycles that are shorter than 21 days			✓
Endometrial cancer (cancer of the lining of the uterus): vaginal bleeding not associated with a period or after menopause; abnormal blood-tinged discharge from the vagina; pain in the pelvis			✓

Serious side effects and what to do about them			
	Talk to your healthcare professional		Stop taking drug and get immediate medical help
Symptom / effect	**Only if severe**	**In all cases**	
Gallbladder problems: fever, nausea, pain that radiates to your shoulder or back, severe pain in your upper right abdomen, vomiting	✓		
Liver problems: yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, light coloured stool, unusual tiredness		✓	
Neuritis (inflammation of the nerve): pain, feeling of pins-and needles, numbness, loss of reflexes		✓	
Palpitation (fast-beating, fluttering or pounding heart): heart skipping beats, beating too fast, pounding, fluttering rapidly			✓
Restless Legs Syndrome: uncontrollable urge to move your legs typically occurs in evening or during the night when sitting or lying down	✓		
Urinary tract disorders: difficulty and pain when passing urine, blood in urine		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at room temperature between 15°C - 25°C.
- Store in a dry place. Do not refrigerate.
- Protect from light by keeping the dial-pack inside the outer carton.
- Keep out of the reach and sight of children

If you want more information about Activelle® LD:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for health professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.novonordisk.ca; or by calling 1-800-465-4334.

This leaflet was prepared by Novo Nordisk Canada Inc.

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